



Design and Selection of Novel Kinase Inhibitors Implicated in Alzheimer's Disease by High Throughput Virtual Screening

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Authors' contributions

This work was carried out in collaboration between both authors. Both authors read and approved the final manuscript.

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ABSTRACT

CDK5 (cyclin dependent kinase 5) is a promising target for treating a variety of neurodegenerative illnesses. The discovery of effective and selective CDK5 inhibitors that engage the polar side chains of the ATP-binding pocket as well as establish specific hydrogen bonds with the kinase has made significant progress. To find novel prospective CDK5 inhibitors with improved effectiveness, ADME characteristics, and a large margin of safety. High throughput virtual screening employing flexible docking was used to screen 2,50,000 compounds from the Specs database against the CDK5 crystal structure (PDB ID: 1UNL). The docking simulation was performed using HTVS first, then SP, and finally XP. The interaction pattern to the receptor with fresh lead candidates has been found and selected based on the GLIDE docking score. The lead moiety in the co-crystallized roscovitine with CDK5 complex retains critical H-bonding patterns while also introducing hydrophobic interactions with Ile10 and Leu133. Selected hits demonstrate hydrophobic interactions with Asn 144, Gly 13, and Ala143 within the ATP cleft in a comparable way to reference compounds (Roscovitine). The lead compound's binding pattern revealed by GLIDE docking experiments demonstrated that molecules bind to the kinase's well-conserved catalytic pocket.

Keywords: Roscovitine; ADME; docking; neurodegenerative.

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1. INTRODUCTION

Cyclin dependent kinases (CDKs) are a broad family of proline-directed serine/threonine kinases that play a key role in the control of cellular progression by modulating various events during the cell cycle [1]. The interaction of the CDK5 subunit with its regulatory subunit cyclin generates CDK5 activity. A variety of cdk5 have been found and described based on their binding capability. The CDK family consists of 20 CDKs, according to a recently established nomenclature [2]. Cyclin dependent kinase is encoded by roughly 21 genes in the human genome. CDK1 is required for cell division and helps to prevent embryonic death. CDK2, CDK4, and CDK6 are essential for the proliferation of specialised cells that do more than only control the cell cycle [3]. CDK5 is important for the development of the central nervous system. For kinase activation, CDK5 must be associated with a regulatory partner. In mammals, the regulating neuronal proteins p35 and p39 activate CDK5 [5,6]. To develop functional circuits capable of expressing synaptic plasticity, the CNS requires the automatic migration, differentiation, and connection of neurons. CDK5 is essential for all of these stages of CNS development, according to several studies. CDK5 null mutant mice, as well as p35/p39 double null mutant mice, have aberrant cortical laminar architectural problems in the cerebellum, brainstem, and hippocampus, according to Ohshima et al. 1996 and Ko et al. 2001. CDK5 is thought to have a significant role in neuronal migration based on these anatomical results. Neuronal migration has been related to CDK5-mediated phosphorylation of a wide spectrum of substrates, including proteins involved in cytoskeletal dynamics and axonal transport. CDK5 has been linked to neuronal differentiation, according to Cicero and Herrup et al. 2005. When CDK5 is missing during development, neurons are unable to exit the cell cycle, resulting in incomplete differentiation. CDK5 has been linked to the connectivity of developing neurons by Kwon et al. 1999 and Hahn et al. 2005. CDK5 impacts on growth cone collapse and neurite actin dynamics, as well as disturbed fasciculation of axonal tracts like the corpus callosum in p35 null mutant mice, providing evidence for a function of CDK5 in axon guidance. CDK5 appears to play a critical part in corticogenesis, as evidenced by studies that suggest it promotes migration by acting positively on pro-migratory signals and perhaps by antagonising anti-migratory signals. CDK5 has been discovered as a neuroblast migratory

regulator in the postnatal subventricular zone [5]. Neurite outgrowth is inhibited in cultured primary neurons when CDK5 activity is reduced by expressing dominant-negative CDK5 mutants or employing antisenseoligonucleotides of Cdk5, p35, or p39 [6]. CDK5 is also involved in the regulation of excitatory ionotropic glutamate receptors, which are crucial for learning. CDK5 also mediates connections between calpain and the NMDA Receptor's NR2B subunit. Conditional CDK5 deletion in adult mice increases hippocampal-dependent learning and plasticity by disrupting the calpain/NR2B complex, which results in increased levels of NR2B at the synapse [7]. Interestingly, the enhanced cognition and plasticity area accompanied by elevations in basal excitability and contribute to the development of epileptic form activity and audiogenic seizures [8], supporting CDK5's role in tonal repression and baseline maintenance in neurons.

2. STRUCTURE OF CDK5

CDK5/p25 was first crystallised in a monoclinic space group, and its structure was established with a resolution of 2.65 [9]. The CDK5D/p25 monoclinic crystal structure was employed for a complex molecule whose pharmacological and modelling implications were recently disclosed [10,11]. The monoclinic crystals had a plate-like shape, grew in stacks, and were very brittle, making the handling necessary for comprehensive inhibitor screening extremely difficult. A novel flexible methodology for determining the structure of ATP-competitive inhibitors coupled to the CDK5/p25 active site is now available. This compound has a particularly good diffracting crystal shape that routinely provides high-resolution X-ray diffraction data. This new technology is a great complement to crystals of CDK2 and the CDK2/cyclin A complex, since it allows researchers to better understand how CDK inhibitors attach to the CDK active site. CDK5/p25 crystals might be a viable alternative to CDK2 crystals for all inhibitors that have been unable to co-crystallize with CDK2 due to technological constraints [12]. Large databases of crystallographic models of small molecule inhibitors bound into the active site of various CDK family members may potentially give helpful information on structural differences that should be used for the construction of selective inhibitors. The CDK5/p25 complex's interaction with (R)-roscovitine in the CDK5 active region provides a model for comparison with previously described

CDK2 structures [13-15]. The structure also revealed that CDK5 that had previously been phosphorylated on Tyr15 was more susceptible to inhibition by (R)-roscovitine than its unphosphorylated cousin. The structures show that phosphorylation of Tyr15, which activates CDK5, does not make the CDK5/p25 complex any less vulnerable to (R)-roscovitine inhibition. It also implies that the conformational space traversed by the kinase might be used to produce medications that target certain kinase conformations (activation states). These could include conformations caused by other protein ligands, such as p35, p39, or Cables in the case of Cables. The binding of Gleevec to the active site of Abl [16] is the greatest example of this idea. The inhibitor forces the activation loop into an inactive conformation in the complex of Gleevec with Abl, in which the conserved DFG motif at the loop's entry is diverted from its usual conformation, causing the phenylalanine to point into the ATP-binding site and the aspartate to no longer coordinate the magnesium. Roscovitine, aloisine, and indirubin, the inhibitors disclosed in this study, are substantially smaller than Gleevec and are unable to bridge the distance to the activation region. As a result, in the presence of these inhibitors, this segment (and the DFG motif in particular) does not modify its structure in comparison to the uninhibited structure.

CDK5 is shown in gray, p25 in blue. The ATP-binding pocket between the N and C terminal lobes of the kinase is occupied by (R)-roscovitine (yellow) [9].

3. REGULATION OF CDK5

P35 is the most well-known CDK5 activator. It has a length of 307 amino acids and a mass of 35 kDa, and is divided into two regions: N-terminal, which has 98 amino acids and contains a myristoylation signal important for p35 membrane targeting [17], and C-terminal, which has 209 amino acids and contains the p25 region, as well as a Proline rich stretch and a Cdk binding and activation domain [18]. A signal for p35 degradation via the Ubiquitin-Proteasome pathway is also present at the N-terminus [19]. P25 assumes a cyclin-like structure, and when CDK5 binds to it, it adopts a conformation that is nearly identical to that of active CDK2. P25/crystal cdk5's structure suggests post-translation phosphorylation and dephosphorylation, which differs from CDK1 and CDK2 [20]. The co-crystallized structure also inform that p25 contain residue essential for

substrate specificity of CDK5 and the availability of its regulatory activator is only rate limiting step in CDK5 activation process [21].

4. DEREGULATION OF CDK5

CDK5 has been suggested as a possible link between A toxicity, tau pathology, and neurodegeneration [20]. Various neurotoxic conditions, such as ischemic brain injury, oxidative stress, excitotoxicity, and amyloid peptide therapy of primary neurons, result in the formation of p25 segment from p35 cleavage [22-24]. Phosphorylation of p35 seems to protect it from Calpain cleavage [25-26].

5. PHOSPHORYLATION OF TAU BY CDK5

Tau is a microtubule associated protein (MAP) that affects microtubule formation and stability in neurons. Tau synthesis, along with Tubulin synthesis, is upregulated during neuronal development in adult neurons, notably in the axon [27]. The main function of MAP Tau is to keep microtubules stable. The presence of a microtubule binding domain, which is made up of repetitions of highly conserved Tubulin binding motifs, distinguishes tau structurally. The "Projection Domain"[28] has a C-terminal with a basic proline-rich area and an acidic N-terminal. Cdk5 phosphorylates Tau on S202, T205, T212, T217, S235, S396, and S404, according to phosphor-epitope specific antibodies, phosphor-peptide mapping, and mass spectrometric analysis [29-32].

6. ROLE OF CDK5 IN AMYLOID PRECURSOR PROTEIN

Amyloid Precursor Protein (APP) is a type-1 transmembrane glycoprotein with a 770-residue extracellular domain and a short carboxy terminus in the cytoplasmic domain [33]. A single copy gene on the mid part of human chromosome 21's long arm codes for APP [34]. The releasing of Fibrillogenic AB peptide is caused by sequential cleavage of APP by - Secretase (BACE 1) in the ectodomain and - Secretase [35]. Another prominent hallmark of AD pathogenesis is increased AB synthesis and extensive Amyloid plaque owing to extracellular AB peptide deposition. CDK5 phosphorylates APP in the cytoplasmic domain on Thr 668 [36]. Phosphorylation of Thr 668 influences APP's binding to the cytoplasmic adaptor protein FES

[37], indicating that phosphorylation of this residue is important for appropriate APP function. Thr 668 phosphorylated APP is upregulated in AD brain tissue, where it is concentrated in

endocytic vesicles, according to a recent study. CDK5 inhibitors prevent Thr 668 phosphorylation, which leads in a significant decrease in amyloid-peptides [38].

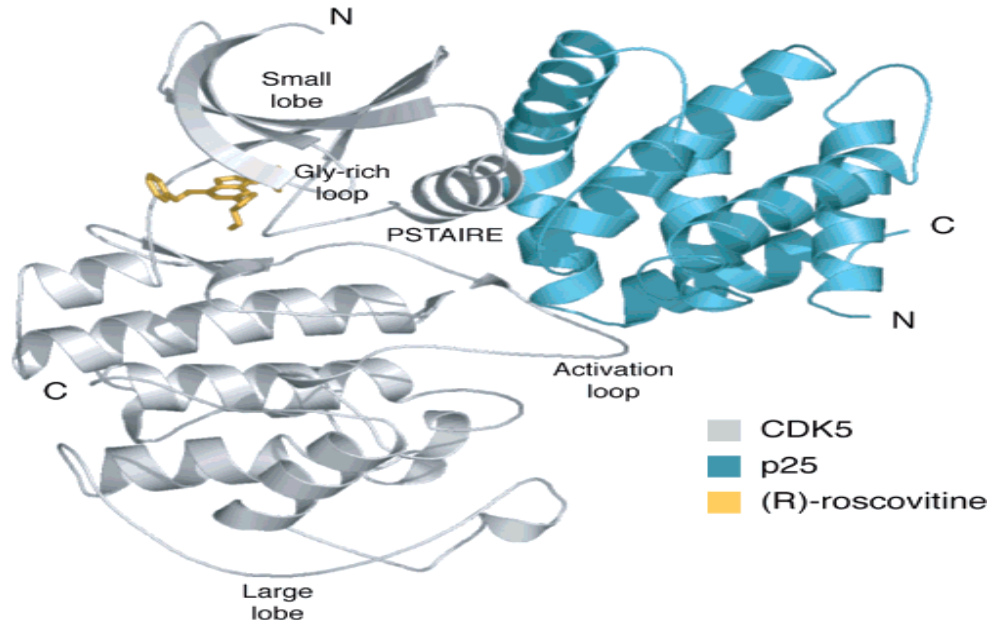


Fig. 1. Ribbon diagram of the CDK5/p25 complex

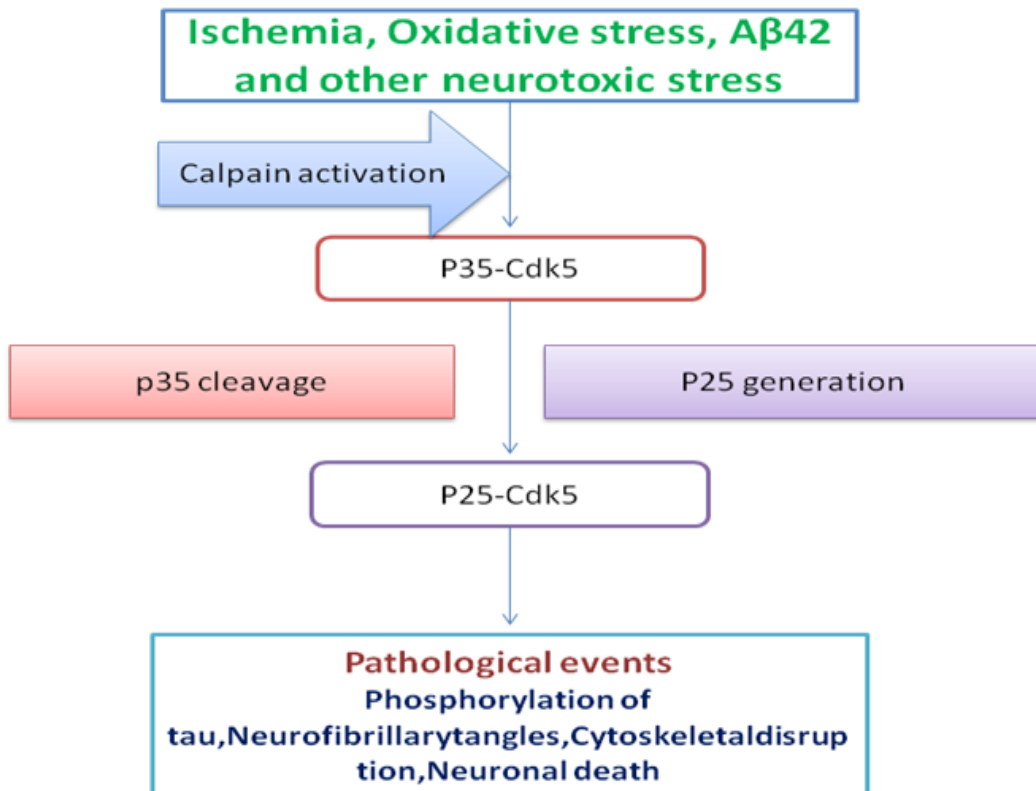


Fig. 2. The deregulation of CDK5 activity

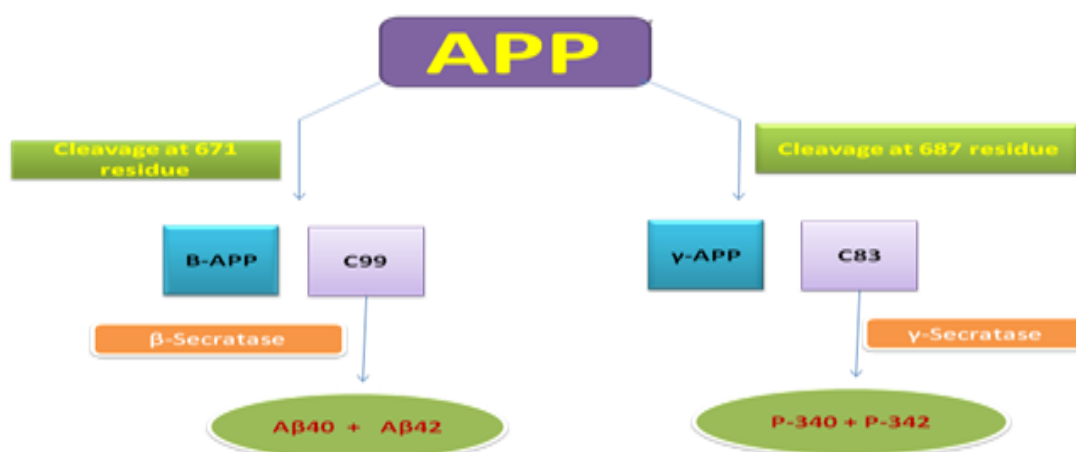


Fig. 3. Processing of Amyloid precursor protein

7. MATERIAL AND METHODS

7.1 Docking Studies

Docking against the crystal structure of CDK5 using Glide was used to screen the Specs database (library of chemicals). Glide looks for interactions between one or more ligand molecules and a receptor molecule, which is commonly a protein. Each ligand is a single molecule, however the receptor may contain many molecules, such as a protein and a cofactor. Glide was used in rigid or flexible docking modes, with the latter generating conformations for each input ligand automatically. A ligand posture is the combination of a ligand's location and orientation relative to the receptor, as well as its shape in flexible docking. Glide's ligand poses go through a set of hierarchical filters that assess the ligand's interaction with the receptor. The initial filters use a grid-based technique modelled after the empirical Chem Score function to assess the spatial fit of the ligand to the designated active site and to examine the complementarity of ligand-receptor interactions. The last stage of the procedure includes evaluating and minimising of a grid approximation to the OPLS-AA non bound ligand-receptor interaction energy. The energy-minimized poses are then scored in the final round. The docking simulation was completed in three stages:

1. HTVS (high-throughput virtual screening) docking—High-throughput virtual screening docking is used to quickly test a large number of ligands. HTVS provides far fewer conformational sampling options

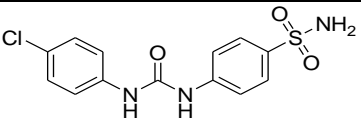
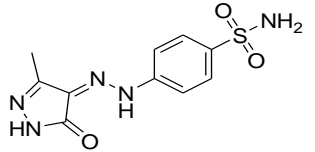
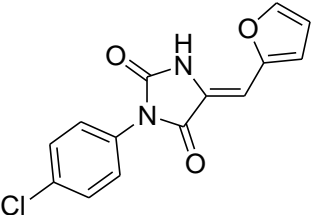
than SP docking, and it can't be utilised with score-in-place or stiff docking. For HTVS, advanced options are not accessible; instead, established defaults are used.

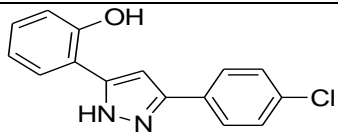
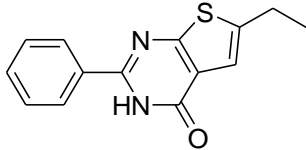
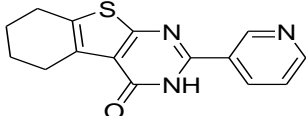
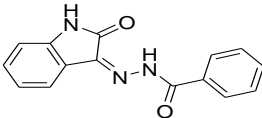
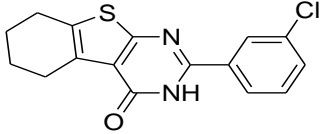
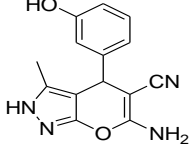
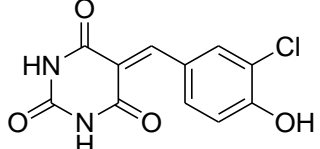
2. SP (standard precision) - Standard-precision docking is useful for screening a large number of ligands of uncertain quality. The default precision is standard. XP (extensive precision)
3. The extra-precision (XP) mode of Glide combines a robust sampling technique with the usage of a unique scoring function based on well-known physical chemistry concepts to detect ligand poses that would be predicted to have unfavourable energies. Only active compounds are expected to have postures available that avoid these penalties while also receiving acceptable scores for suitable hydrophobic contact between the protein and the ligand, hydrogen-bonding interactions, and other factors. The XP method's main goals are to eliminate false positives and improve the link between excellent poses and good results. Extra-precision mode is a refining technique that should only be used on ligand poses that are in good shape. Finally, Schrödinger's unique Glide Score scoring system is used to re-score the reduced postures. Glide Score is similar to Chem Score, but it contains a steric-clash term and Schrödinger's buried polar terms to punish electrostatic incompatibilities.

$$\text{Glide Score} = 0.065 \cdot \text{vdW} + 0.130 \cdot \text{Coul} + \text{Lipo} + \text{Hbond} + \text{Metal} + \text{BuryP} + \text{RotB Site}$$

Table 1. Glide Score components

Component	Description
vdW	Van der Waals energy. This term is calculated with reduced net ionic charges on groups with formal charges, such as metals, carboxylates, and guanidiniums.
Coul	Coulomb energy. This term is calculated with reduced net ionic charges on groups with formal charges, such as metals, carboxylates, and guanidiniums.
Lipo	Lipophilic contact term. Rewards favourable hydrophobic interactions.
HBond	Hydrogen-bonding term. This term is separated into differently weighted components that depend on whether the donor and acceptor are neutral, one is neutral and the other is charged, or both are charged.
Metal	Metal-binding term. Only the interactions with anionic acceptor atoms are included. If the net metal charge in the apo protein is positive, the preference for anionic ligands is included; if the net charge is zero, the preference is suppressed.
BuryP	Penalty for buried polar groups.
RotB	Penalty for freezing rotatable bonds.
Site	Polar interactions in the active site. Polar but non-hydrogen-bonding atoms in a hydrophobic region are rewarded.

S.NO	Hit	Structure	IUPAC NAME	Glide score
1	SKD-H1		4-[[[(4-chloroanilino)carbonyl]amino]benzenesulfonamide	-12.040736
2	SKD-H2		4-[2-(3-methyl-5-oxo-1,5-dihydro-4H-pyrazol-4-ylidene)hydrazino]benzenesulfonamide	-11.229700
3	SKD-H3		3-(4-chlorophenyl)-5-(2-furyl methylene)-2,4-imidazolidinedione	-9.593023

S.NO	Hit	Structure	IUPAC NAME	Glide score
4	SKD-H4		2-[3-(4-chlorophenyl)-1H-pyrazol-5-yl]phenol	-9.286539
5	SKD-H5		6-ethyl-2-phenylthieno[2,3-d]pyrimidin-4(3H)-one	-9.224028
6	SKD-H6		2-(3-pyridinyl)-5,6,7,8-tetrahydro[1]Benzo thieno[2,3-d]pyrimidin-4(3H)-one	-9.194986
7	SKD-H7		N'-(2-oxo-1,2-dihydro-3H-indol-3-ylidene)benzohydrazide	-9.123951
8	SKD-H8		2-(3-chlorophenyl)-5,6,7,8-tetrahydro[1]benzothieno[2,3-d]pyrimidin-4(3H)-one	-9.077507
9	SKD-H9		6-amino-4-(3-hydroxyphenyl)-3-methyl-2,4-dihydropyrano[2,3-c]pyrazole-5-carbonitrile	-8.692094
10	SKD-H10		5-(3-chloro-4-hydroxybenzylidene)-2,4,6-(1H,3H,5H)-pyrimidinetrione	-8.428099

7.1.1 Knowledge based selection of top scoring compounds

The resultant conformations/poses of the ligands at the binding site of 1UNL were analysed after the screening procedure was completed, and per residue H-bond, hydrophobic, and interaction patterns within 15 Å⁰ region from centre of grid were studied. The ligand-receptor binding interaction pattern and glide docking score were investigated using the results of a Specs database screening.

8. CONCLUSION

By creating a CDK5 active site homology model, powerful CDK5 inhibitors such as Benzthiazole, Quinoline, Triazole, Benzimidazole, and Pyridine may be further explored and optimised. Because of its role in numerous neurodegenerative pathways, it's reasonable to believe that CDK5 could be a useful pharmaceutical target for preventing or even arresting these diseases. The chemicals used in this work might be used as molecular probes to learn more about CDK5's function in neurodegenerative diseases therapy. We obtained a better grasp of the structural needs and constraints for the manufacture of selective CDK5 inhibitors as a result of our research. To summarise, in order to increase the performance and precision of docking simulation based screening, first HTVS screening was done, followed by SP and XP screening. Initially, the Specs database library of compounds was screened using HTVS-based flexible docking to allow for quick sorting of ligands with very low affinity to the binding site (grid active site residues), followed by SP and XP docking to improve docking precision by optimising functional group binding interactions to the active site residues.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

Competing interests

Authors have declared that no competing interests exist.

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